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Effect of Spiromesifen on Oxidative Stress in Bronchial Epithelial Cells

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ABSTRACT

This study aims to investigate the cytotoxic and oxidative effects of Spiromesifen, a widely used new generation insecticide, on human bronchial epithelial cells, BEAS-2B. The colony formation test was conducted to assess the impact of spiromesifen on cell viability. The oxidative stress state was assessed by measuring Total Oxidative Stress (TOS), Malondialdehyde (MDA), and Glutathione (GSH) levels at concentrations of 12.5, 25, and 50 µM over time. The results indicated that spiromesifen treatment markedly diminished cell viability in a dose- and time-dependent manner with an IC_{50} value of 100 µM. Following 72 hours of treatment, a statistically significant elevation ($p < 0.05$) in TOS and MDA levels, indicative of lipid peroxidation, was seen across all concentrations. Conversely, GSH levels, integral to the cellular antioxidant defence system, were observed to be markedly diminished across all concentrations. This study concludes that spiromesifen displays cytotoxicity in human cells, alters cellular redox equilibrium by producing oxidative stress, and causes irreversible molecular damage through lipid peroxidation.

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1. Introduction

The Environmental Protection Agency (EPA) defines pesticides as toxic substances or biological agents intentionally released into the environment to control and kill pests, including weeds, insects, rodents, and fungi. The use of pesticides has increased over the years. Pesticides are used in various forms (sprays, powders, etc.) not only in agriculture but also in homes to kill harmful pests. Therefore, our indirect exposure to these substances has increased as they are present in the air we breathe and the food we eat. People may come into direct contact with pesticides

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(during their preparation and use) and/or indirect contact (by inhaling residual air concentrations or being exposed to residues on surfaces, food, dust, etc.) (Ataei & Abdollahi, 2022). Pesticides are considered potential chemical mutagens. Studies showing that various agricultural chemicals possess mutagenic properties that cause mutations, chromosomal changes, or DNA damage have been known for a long time. Genetic damage associated with pesticides occurs in human populations exposed to high dose levels due to intensive use, misuse, or failure of control measures (Bolognesi, 2003).

Spiromesifen (3-mesityl-2-oxo-1-oxaspiro[4.4]non-3-en-4-yl 3,3-dimethylbutonate) is a new generation insecticide, which utilized since the mid-2000s, belonging to the spirosyclic tetronic acid class. It acts as an inhibitor of acetyl-CoA carboxylase, a lipid metabolism enzyme, causing a significant reduction in total lipids (Kontsedalov et al., 2009; Bielza et al., 2019; Cerda-Apresa et al., 2024). Various agricultural products containing this active ingredient are widely used worldwide under license for the control of the two-spotted spider mite (*Tetranychus urticae*), cotton spider mite (*Tetranychus cinnabarinus*) and tobacco whitefly (*Bemisia tabaci*) are licensed and widely used worldwide (EFSA, 2012; Ruiz-Guzmán et al., 2017; Yorulmaz Salman & Kaplan, 2014). The agricultural pests targeted by spiromesifen (SPF) include species with documented resistance to other insecticides/acaricides or invasive species capable of acting as disease vectors. Furthermore, it has been reported that this substance may be more beneficial to users because it exhibits lower toxicity to non-target organisms compared to other pesticides in integrated pest management (EPA, 2020; 2022). For these reasons, the use of SPF is rapidly increasing, as is the case with other pesticides.

In actuality, SPF may not be as harmless as anticipated in terms of toxicity. In its 2021 report assessing the potential ecological and human health risks of SPF use, the EPA states that the frequency of use and application dose can be reduced, and different application methods should be used to minimise the potential effects of the substance (EPA, 2020). This is because SPF has been reported to have low acute oral, dermal, and inhalation toxicity in rats. Furthermore, the ecotoxicological risk assessment classifies SPF as highly toxic to fish and aquatic invertebrates (EFSA, 2012). It has been reported that bees are also affected by SPF; histopathological and cytotoxic changes were observed in the midgut of exposed bees (Serra et al., 2021). A study conducted on the Na2 mouse neuroblastoma cell line also reported that SPF at high concentrations causes neurite inhibition, reduces proliferation, and decreases the viability of cultured neurons. Researchers indicate that this substance is moderately toxic to neurons by increasing oxidative stress and apoptosis (Karakayali et al., 2021). In the only one study with human cells in the literature, it has been reported that SPF exposure damages the cytoskeleton, causes cell cycle arrest, and impairs the viability and migration of human umbilical vein endothelial cells. The same study also reported that SPF contributes to vascular developmental toxicity by disrupting cell proliferation and migration in zebrafish embryos (Wang, Liu, Wang & Hu, 2022). As seen, although the genotoxic effects of the SPF have been demonstrated in various organisms, studies evaluating its genotoxic and cytotoxic effects on human cells are quite limited (Kontsedalov et al., 2009; Horibe et al., 2018; Rajaee et al., 2022).

Exposure to pesticides has been associated for many years with various respiratory pathologies such as asthma, chronic obstructive pulmonary disease, and lung cancer, as well as various respiratory symptoms such as coughing, wheezing, and dyspnea (Pesatori et al., 1994). Lung cancer is one of the most commonly diagnosed cancers worldwide and ranks first among cancer-related deaths (Smith & Glynn, 2000; Alavanja et al., 2004;). It has also been known for many years that lung cancer is positively associated with the use of herbicides and insecticides (Barthel, 1981; Roos et al., 2016; Kangkhetkron & Juntarawijit, 2022).

The cytotoxic effects and oxidative stress effects of SPF on human lung epithelial cells were examined in this study due to the well-established high correlation between pesticide use and cancer and the widespread use of the pesticide, as well as the paucity of research on the subject. We investigated the effects of SPF on cytotoxicity via the clonogenic test. Changes in MDA, GSH, and TAS parameters were investigated to evaluate the effects of SPF on oxidative stress.

2. Material and Method

2.1. Chemicals

SPF (Cat. No: 33599), Triton X-100, paraformaldehyde, tris base, ethylenediaminetetraacetic acid, and DMSO were purchased from Sigma-Aldrich; Merck KGaA (Darmstadt, Germany). RPMI media, fetal bovine serum, trypsin/EDTA solution, phosphate-buffered saline, penicillin-streptomycin (Gibco; Thermo Fisher Scientific, Inc., Waltham, MA, USA). Tissue culture flasks and plates were purchased from Corning. MDA assay kit (Cat. No: E0017Ge), and GSH assay kit (BT LAB, Cat. No: EA0021Ge) were purchased from BT LAB (Jiaxing, Zhejiang, China). TOS assay kit (Cat. No: E-BC-K802-M) was purchased from Elabscience (Wuhan, China).

2.2 Methods

2.2.1. Cell culture and maintenance

BEAS-2B, a human lung epithelial cell line, was used in the present study. Dr. John Wise of the University of Louisville in the United States generously donated the cell line. The cells were developed in RPMI medium and incubated at 37 °C in a humidified atmosphere with 5% CO_2. Prior to cell seeding, attachment factor protein was applied to all tissue culture-treated plates, flasks, and chambers (Şekeroğlu et al., 2021). Every experiment was performed in triplicate.

2.2.2. Determination of cell viability with clonogenic assay

After seeding BEAS-2B cells at a density of 1 x10^5 cells/well in each well of a 6-well plate to assess colony-forming potential, the cells were treated with different concentrations of SPF (0, 5, 12.5, 25, 50, 75, and 100 µM) for 72 hours. The SPF concentrations to be applied were prepared using a 100 mM stock SPF in DMSO and dilutions were carried out with dH_2O. As previously reported (Şekeroğlu et al., 2021), BEAS-2B cells were tested for their capacity to form colonies in a culture dish. After 72 hours of treatment, the cells were collected and replated at a density of 5000 cells per 60 mm dish.

The cells were thereafter allowed to multiply and establish colonies. Subsequent to the establishment of colonies, they were fixed with methanol. Then the crystal violet used to stain the formed colonies. Three plates were cultivated for each treatment, and the trials were conducted three times. Plating efficiency was calculated using the formula: plating efficiency = number of colonies obtained / number of cells planted. Logarithmic regressions were conducted to ascertain IC_{50} values. All results were presented as percentage inhibition compared to control cells, which were designated as 100%.

2.2.3. Oxidative stress parameters

Levels of glutathione (GSH), malondialdehyde (MDA), and total oxidant status (TOS) were evaluated using ELISA kits, following the respective manufacturers' instructions: MDA (BT LAB, Cat. No: E0017Ge), GSH (BT LAB, Cat. No: EA0021Ge), TOS (Elabscience Cat. No: E-BC-K802-M). Each sample was analysed in triplicate.

2.2.4. Statistical analysis

The data displays the mean ± standard error (SE) of a minimum of three independent experiments. The student's two-tailed t-test and two-way ANOVA analysis were conducted using GraphPad Prism 8 software (San Diego, CA, USA). *P*-values were deemed statistically significant if they were less than 0.05.

3. Results and Discussions

Following SPF treatment, fewer colonies were created by surviving cells. All administered SPF concentrations considerably decreased the colony formation, with concentrations of 12.5 µM and above demonstrating statistical significance in comparison to the control group after 72 hours of treatment ($p<0.05$) (Figure 1). Based on these findings, 100 µM has been identified as the IC_{50}. For subsequent research, a maximum dose of 50 µM, a medium dose of 25 µM, and a low dose of 12.5 µM were established, respectively.

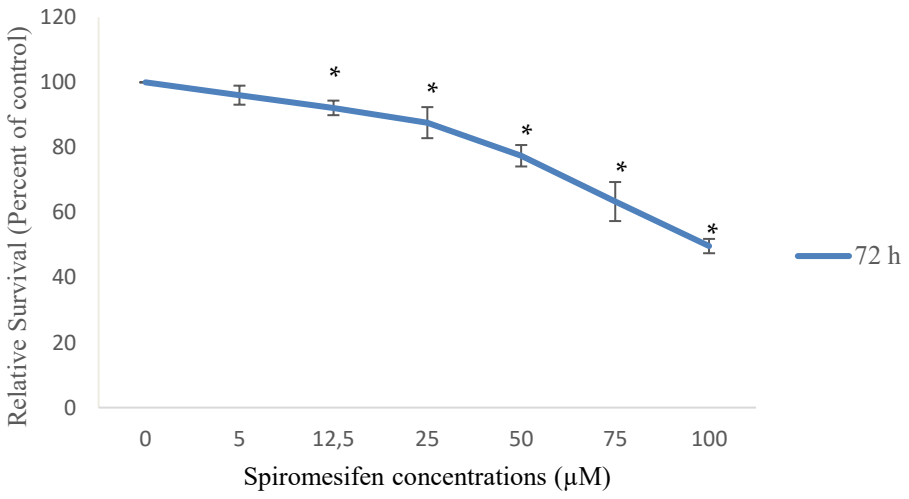

Figure 1. Spiromesifen's effects on BEAS-2B cell viability. Three separate experiments' mean ± SE is represented in the data. *$p < 0.05$ compared to the control.

A significant advantage of the clonogenic approach is its capacity to ascertain long-term survival effects that other viability assays fail to identify. In contrast to short-term viability assessments, clonogenic assays permit prolonged observations of cell morphology and clonogenicity in contexts where alternative approaches fail to ascertain the long-term impact on cell viability and clonogenic capacity (Garg et al., 2018). These findings demonstrate that spiromesifen adversely impacts both cell survival and reproductive capacity.

SPF exposure has been shown to elevate total oxidative stress in cells in a dose- and time-dependent manner. Concentrations of 25 µM and 50 µM SPF resulted in a significant increase of TOS levels in treatments enduring 24, 48, and 72 hours. The 12.5 µM SPF concentration, however, exhibited a significant reduction only after 72 hours of treatment (Figure 2).

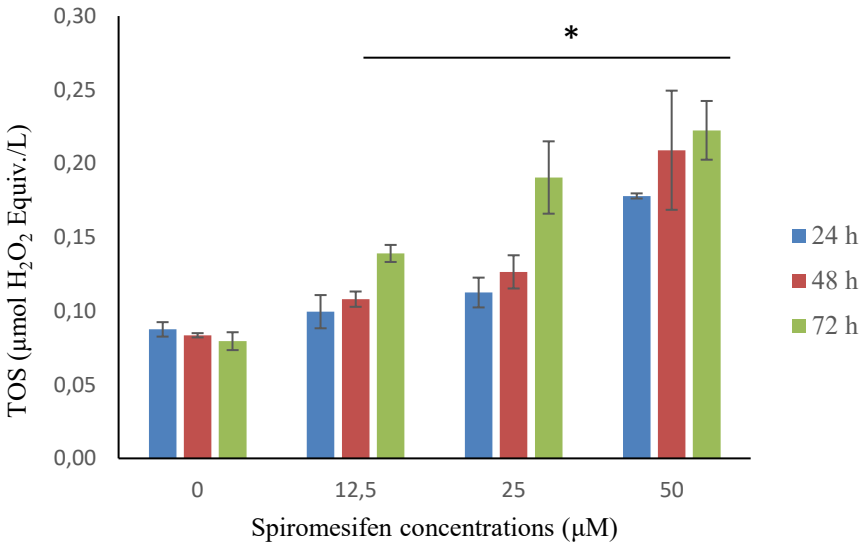

Figure 2. Quantitative analysis of TOS demonstrating increased oxidative stress in treated cells compared with control. Three separate experiments' mean ± SE is represented in the data. *$p < 0.05$ compared to the control.

After 72 hours of exposure, the GSH parameter, which informs us about the ability of cells to defend against oxidative stress, significantly decreased at all concentrations (Figure 3).

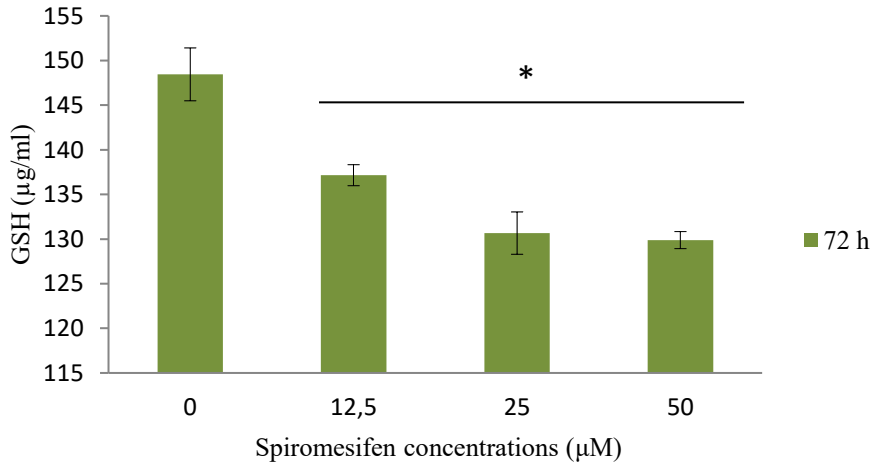

Figure 3. Graphical representation of GSH levels showing significant depletion compared with the control group. Three separate experiments' mean ± SE is represented in the data. *$p < 0.05$ compared to the control.

After 72 hours of treatment, there was a significant rise in MDA, which is thought to be an essential sign of oxidative stress and lipid peroxidation, at all concentrations (Figure 4).

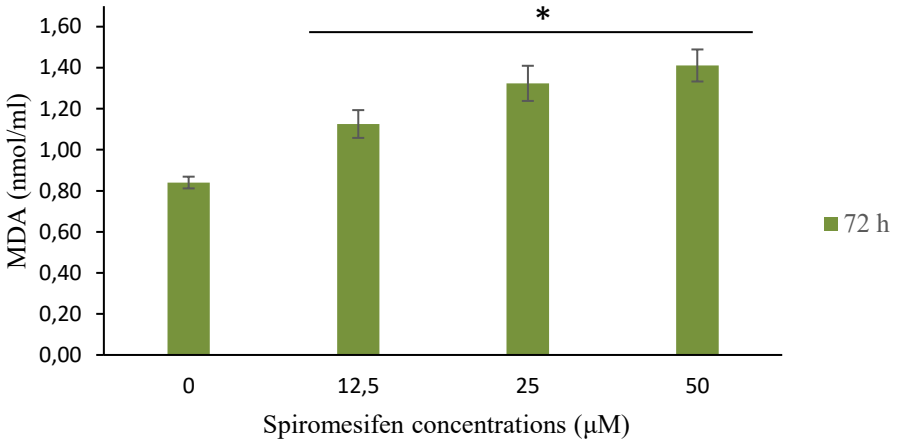

Figure 4. Graphical representation of MDA levels showing significant lipid peroxidation across treatment groups. Three separate experiments' mean ± SE is represented in the data. *$p < 0.05$ compared to the control.

SPF exhibits variable toxicity among various species and routes of exposure, with negative impacts observed through ingestion, inhalation, dermal contact, and ocular contact. Another important component of SPF's toxicity profile is its impact on reproduction and development. In rats, SPF causes dose-dependent reproductive toxicity that is correlated with levels of parental toxicity, but developmental toxicity seems to be associated with maternal toxicity (Hussain & Gaur, 2024).

Bronchial epithelial cells are highly lipogenic, exhibiting a rapid lipid turnover rate to fulfill the requirements for surfactant generation (Yang et al., 2003). The significant demand for lipid production underlines the essential role of lipids in preserving lung structure and function. This circumstance presents lipids as pivotal in lung physiology and disease (Zemski Berry et al., 2017). ACC inhibition not only results in a decrease of fatty acids but also induces extensive alterations in cellular lipid metabolism. Inhibition of ACC leads to the accumulation of lysophospholipids, a reduction in the synthesis of free fatty acids and phospholipids, and alterations in fatty acid composition due to an elevated ratio of polyunsaturated fatty acids (Kim et al., 2023; Gollowitzer et al., 2025). These modifications in the lipid profile may increase cellular sensitivity to oxidative stress due to a decrease in saturated and monounsaturated phospholipid varieties (Wang, Yu, Li, Guo, He & Wang, 2022).

Investigations on non-target organisms have evidenced the negative effect of spironolactone on cellular viability and oxidative stress parameters Although there was no direct mortality inhoneybees (*Apis mellifera*), exposure to SPF caused histological and cytological alterations in the midgut, including cell degeneration and disarray of epithelial architecture (Serra et al., 2021). Increased oxidative stress and lipid peroxidation were suggested by elevated catalase activity and malondialdehyde levels in mosquitoes (*Aedes aegypti* L.), underscoring SPIRO's impact on lipid metabolism. Additionally, SPF showed sterilising effects, greatly lowering adult female fecundity and fertility, which affected *Ae. aegypti*'s ability to reproduce (Cerda-Apresa et al., 2024). SPF and its metabolite caused oxidative stress,

increased lysosomal and phagosomal activity, and destroyed epidermal cells, suggesting cytotoxic effects on earthworms (*Eisenia fetida*) (Fang et al., 2022). *In vitro* research on mouse neuroblastoma cells revealed mild neurotoxicity, including decreased cell viability, elevated oxidative stress, and apoptosis at elevated concentrations (Karakayali et al., 2021). SPF exposure, showed cytotoxic effects by interfering with cell survival, structure, and vascular development-related gene expression human umbilical vein endothelial cells, or HUVECs. (Wang, Liu, Wang & Hu, 2022). There was no research on the toxicity of SPF employing other human cell types.

The increase in TOS levels and the parallel rise in MDA levels support the idea that lipid peroxidation increases as a result of oxidative stress (Tsikas, 2017). The decrease in GSH levels despite the increase in TOS values indicates that the antioxidant defence capacity of cells is being depleted (Georgiou-Siafis & Tsiftsoglou, 2023). When GSH decrease and MDA increase are evaluated together, it can be said that lipid peroxidation has increased and the antioxidant system has been suppressed (Hassan & Sayyah, 2023).

This work thoroughly illustrates the cytotoxic and oxidative-damaging effects of SPF exposure on bronchial epithelial cells (BEAS-2B). The results demonstrate that SPF markedly inhibits colony formation by reducing cell viability in a dose- and time-dependent fashion. Specifically, it demonstrates that the SPF treatment disturbs intracellular redox equilibrium. It has been established that exposure elevates TOS. Simultaneously, it has been demonstrated that it elevates MDA levels, a vital marker of lipid peroxidation. Conversely, it has been established that it markedly diminishes GSH levels, a key component of the cell's antioxidant defence system. Upon comprehensive evaluation of the data, it is posited that the cytotoxicity generated by SPF is fundamentally rooted in a pronounced oxidative stress mechanism, instigated by the cells' inadequate antioxidant capability.

4. Conclusions

The toxicity profile poses a potential risk to human health through various exposure routes such as ingestion, inhalation, and dermal contact, and also exhibits harmful effects on non-target organisms. The literature reports that the compound causes cytotoxic effects such as oxidative stress, mitochondrial dysfunction, apoptosis, and cellular degeneration in model organisms such as zebrafish embryos, honeybees, and worms. However, there are no studies directly evaluating the genotoxic potential of SPF. In this context, our study aimed to fill this critical gap and comprehensively examined the cytotoxic and oxidative damage effects of SPF on human bronchial cells (BEAS-2B). Our findings, consistent with the literature, confirmed that SPF reduced cell viability in a dose- and time-dependent manner, ultimately resulting in a decrease in clonogenic ability. In conclusion, this study demonstrates that SPF not only exhibits cytotoxicity in human cells but also disrupts cellular redox homeostasis by inducing oxidative stress and triggering lipid peroxidation, thereby posing a potential genotoxic/cytotoxic hazard. Considering that this significant disturbance in intracellular homeostasis is expected to threaten genomic integrity in the long term, it is essential to conduct genotoxicity and carcinogenesis investigations without delay to elucidate the agent's molecular-level harm potential and associated hazards.

Declaration of Competing Interest and Ethics

The author declares no conflict of interest. This research study complies with research publishing ethics. The scientific and legal responsibility for manuscripts published in OPS Journal belongs to the author.

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